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The underlying hypothesis of our study is that quantitative breast elasticity imaging is possible and provides unique information, which could increase the detection, characterization and monitoring of potentially malignant masses in the breast. The purpose of this study is to develop a new modality of medical imaging for surrogate palpation of deep lying breast lesions, namely Acousto-Mechanical Imaging, or AMI, capable of producing high-resolution images of elastic (Young's or shear) moduli. In our method, the evaluation of mechanical structure and properties of an object is accomplished via the synergy of the surface stress pattern measured by the force sensor array and the internal strain obtained by an ultrasound imager. Acousto-mechanical imaging, therefore, consists of three main components: evaluation of externally induced surface pressure and internal tissue motion; estimation of strain and stress tensor components; and reconstruction of the spatial distribution of the elastic modulus using displacement, strain and stress images. An ambitious research plan has been developed to address important engineering and clinical aspects of AMI. The overall program is designed to critically test the hypothesis that AMI can non-invasively detect and monitor breast lesions thus providing a valuable clinical tool for breast cancer diagnosis, monitoring and therapy.

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INTRODUCTION:

The underlying hypothesis of our study is that remote, non-invasive measurements of breast elasticity are possible and provide unique examiner-independent information, which could increase the detection, characterization and monitoring of potentially malignant masses in the breast. The purpose of this study is to develop a new modality of medical imaging for surrogate palpation of deep lying breast lesions, namely Acousto-Mechanical Imaging, or AMI, capable of producing high-resolution images of elastic (Young's or shear) modulus. In Acousto-Mechanical Imaging, the evaluation of mechanical structure and properties of an object is accomplished via the synergy of the surface stress pattern measured by the force sensor array and the internal strain obtained by the ultrasound imager. Acousto-mechanical imaging, therefore, consists of three main components: evaluation of externally induced surface pressure and internal tissue motion; estimation of strain and stress tensor components; and reconstruction of the spatial distribution of the elastic modulus using displacement, strain and stress images. An ambitious research plan has been developed to address important engineering and clinical aspects of Acousto-Mechnaicl Imaging. The overall program is designed to critically test the hypothesis that Acousto-Mechanical Imaging can non-invasively detect and monitor breast lesions thus providing a valuable clinical tool for breast cancer diagnosis, monitoring and therapy.

BODY:

Breast cancer is a common and deadly disease that metastasises early in its natural history and may recur late [Forrest 1996]. An estimated 203,500 new invasive cases of breast cancer are expected to occur among women in the United States during 2003 [Cancer 2003]. In American women the average lifetime risk of developing breast cancer is about 1 in 8 [Fletcher 1995]. Among the available imaging methods such as mammography, breast ultrasound [Jackson 1995], and magnetic resonance imaging [Hylton 2000], X-ray mammography is considered by physicians to be the gold standard in breast cancer detection, and currently, mammography is the only breast imaging exam approved by the U.S. Food and Drug Administration (FDA) to screen for breast cancer in women who show no signs or symptoms of the disease. However, despite great progress in X-ray mammography, <u>not all cancers</u> are diagnosed in screening or diagnostic mammography – mammography can detect approximately 85 percent of breast cancers. Up to 15 percent of mammogram results are abnormal and require more testing (more mammograms, fine needle aspiration, ultrasound, or biopsy).

As many as 60 percent of palpable breast masses are not visible on mammogram [Pisano 2001]. Palpable breast masses, however, are signalling tissue pathology. This is why one of the arising areas of medical diagnostics is Elasticity Imaging (EI) where either ultrasound or MRI imaging is used to quantitatively map tissue elasticity [Cespedes et al. 1993, Sarvazyan et al. 1998, Emelianov et al. 1995, Chenevert et al. 1998]. Recently, an alternative method of imaging tissue structures in terms of their elasticity, the method of Mechanical Imaging (MI), has emerged [Sarvazyan 1998 and 1999]. The underlying hypothesis of these approaches is that remote, non-invasive measurements of elasticity in

the breast are possible and provide unique examiner-independent information, which could increase the detection, characterization and monitoring of potentially malignant masses in the breast (since changes in soft tissue elasticity are usually related to pathological processes). The purpose of our study was to develop a new modality of medical imaging for surrogate palpation of deep lying breast lesions, namely Acousto-Mechanical Imaging (AMI), capable of producing high-resolution images of elastic (Young's or shear) modulus. AMI includes unique features of both EI and MI, where the data on the stress pattern measured by the force sensor array of MI complement the strain data obtained by ultrasonic EI device. Synergy of these two complementary methods results in superior diagnostic potential of AMI compared to EI and MI separately. Also, for breast imaging, AMI will be used as an important and valuable adjunct to existing ultrasound imaging and mammography.

The evaluation of mechanical structure and properties of an object requires knowledge of the spatial distribution of both stress and strain. The main objective of the work described in this proposal is to utilize strain and stress data measured simultaneously and, consequently, to remotely evaluate the mechanical properties of an investigated tissue with minimal ambiguity. Indeed, ultrasound-based elasticity imaging derives information on tissue elasticity from directly evaluated strain data and using various indirect [Cespedes et al. 1993] or reconstructive [Emelianov et al 1995] methods to estimate necessary stress data. The stress in a real three-dimensional system with localized inclusions is of a complex character, and it is difficult to estimate the stress pattern without direct measurements. Various theoretical assumptions for stress pattern evaluation used in ultrasonic elasticity imaging are not accurate or rigorous and do not provide an adequate description of the mechanical state of the system. The AMI method is free from this shortcoming. The paramount element of an AMI device is a force-sensing array incorporated on the ultrasonic probe surface contacting the tissue. This combined ultrasonic and pressure array probe is, therefore, capable of simultaneous registration of surface stress and internal strain patterns in tissue necessary for subsequent unambiguous and artifact free elasticity imaging. Acousto-mechanical elasticity imaging is performed via the following steps: a) application of controlled deformation to the study object while both real-time ultrasound frames and surface stress patterns are captured; b) phase-sensitive, multi-dimensional speckle tracking and evaluation of internal tissue motion, i.e., measurement of displacement and strain components; and c) reconstruction of the spatial distribution of elastic modulus in the imaging plane using both internal displacement/starin and surface stress data. The goal of acousto-mechanical imaging is to reconstruct maps of tissue Young's modulus using available estimates of displacement/strain/stress components. Elasticity reconstruction algorithms, however, are highly dependent on the signal-to-noise ratio (SNR) of the input data. The higher SNR measurements are used, the higher contrast-to-noise ratio is possible in acousto-mechanical imaging.

Based on the overall needs of breast acousto-mechanical elasticity imaging, including elasticity reconstruction, the strategies for displacement, strain and stress imaging were identified. The results presented here represent the product of past 12 months of work. In the remainder of this section we present detailed results from each of the proposed areas. Please note that no human subjects were part of the original proposal.

Design of pressure sensing array:

The design and development of the pressure-sensing array is of paramount importance for acousto-mechanical imaging (AMI). The pressure-sensing array must be compatible with ultrasound scanner and maintain high resolution and sensitivity while each element remains miniature to allow high-resolution surface stress imaging. After a period of trial and error, we have finally identified Pressure Profile Systems, Inc. (Los Angeles, CA) as the potential supplier of the sensor pad. The Pressure Profile Systems has actively worked with researchers at both the University of Michigan and Artann Laboratories, Inc. (East Brunswick, NJ) to design and fabricate the desired pressure-sensing array. One of such arrays, fully interfaced with ultrasound transducer is presented in Fig. 1, where the ultrasound imaging transducer is enclosed into assembly containing 4 rows of 16 pressure sensors – 2 rows on each side of the transducer – extending the entire lateral dimension of the ultrasound imaging array.

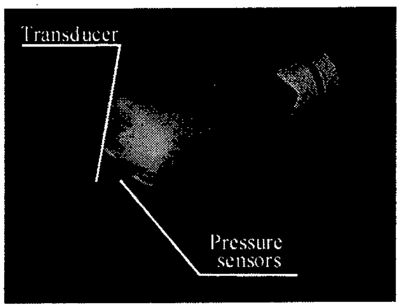

Figure 1: Photograph of the ultrasound transducer interfaced with the pressure-sensing array.

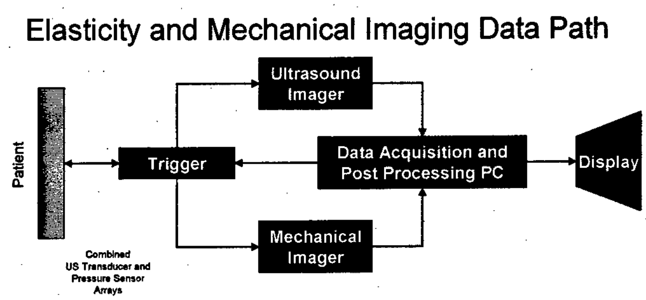

Figure 2: Data path of AMI system built during the project.

The prototype of acousto-mechanical imaging system is illustrated in Fig. 2. The signals from the entire array of pressure sensors can be acquired at 108 frames per second simultaneously with real-time ultrasound frames. The mechanical imaging system is interfaced with a computer that is capable of displaying surface stress maps in real-time. In the second phase of the project, the combined ultrasound transducer array and pressure sensor array was fully interfaced with a computer that is used to capture both ultrasonic and pressure data during the AMI study (Fig. 2). In addition, the same computer is then used to process captured data and produce AMI images of breast.

Stress and Strain Imaging:

To demonstrate how the acousto-mechanical imaging system can detect and quantify absolute elasticity distribution, the experiment performed on polymer-based phantom containing a single hard circular inclusion is presented in Fig. 3. During the deformation of the phantom, frames of both ultrasound data and surface stress were collected.

High SNR strain and stress images were obtained using large (more than 5%) surface deformations. We have developed algorithms to properly measure internal deformations and surface stresses. The major source of noise in displacement/strain measurements is related to strain-induced decorrelation, that is, if the tracking is performed between two frames with significant (more than several percent) internal strain, the resulting displacement and, therefore, strain estimates will have significant

errors. To overcome this limitation, a method of tracking displacement over large displacement ranges was previously developed showing significant signal-to-noise (SNR) improvement in both displacement and strain estimates. The philosophy behind this approach is the capture and retrospective processing of a large set of real-time frames acquired during large surface deformations. Each frame of the dataset contains phase-sensitive ultrasound signals and corresponds to incremental deformation, while the entire dataset spans large internal deformations. Similarly, surface stress patterns aquired at each incremental deformation can be also post-processed to improve stress SNR. Clearly, for acousto-mechanical imaging of breast, this approach is possible and, therefore, high SNR displacement, strain and stress images can be routinely obtained (Fig. 3a).

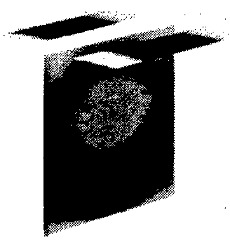

Fig. 3A: Demonstration of simultaneous collection of stress and stain data

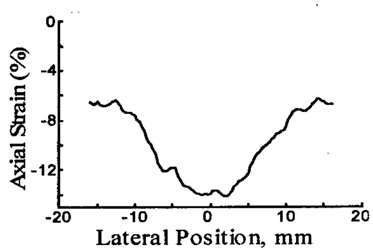

Fig. 3B: Magnitude of axial strain at the surface of the phantom.

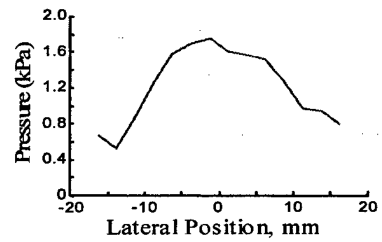

Fig. 3C: Axial stress distribution at the surface of the phantom.

In our approach, once the deformation dataset (frames of ultrasound and surface stress patterns) is non-destructively captured, off-line strain and stress processing is performed. For strain imaging, the first step in the off-line processing is to estimate the motion between two (not necessarily adjacent) frames. The frame-to-frame motion is estimated using a two-dimensional correlation-based phase-sensitive speckle tracking technique. Our particular technique combines the ability of correlation-based algorithms to track relatively large internal displacements with the precision of phase sensitive methods. First, frame-to-frame lateral and axial displacements are estimated from the position of the maximum correlation coefficient, where a correlation kernel approximately equaling the speckle spot is used for optimal strain estimation. The axial displacement estimate is then further refined by determining the zero crossing position of the phase of the analytic signal correlation. Frame-to-frame displacement error is also reduced using a weighted correlation sum and by filtering spatially adjacent correlation functions prior to displacement estimation. Finally, frame-to-frame estimates are added to produce high SNR displacement and strain images of the object. In stress imaging, the captured surface stress patterns are co-registered with ultrasound frames since the data is captured simultaneously. The individual stress estimates were improved by fitting the measured stress at each sensor to a higher order polynomial function thus reducing or eliminating the influence of electronic noise and increasing SNR of stress images.

Elasticity Imaging:

The goal of elasticity reconstruction in acousto-mechanical imaging is to estimate an unknown distribution of Young's modulus based on the simultaneous and synchronized measurement of normal stress at the surface $S_{\sigma u}$ and internal displacement within the ultrasound imaging plane S_I (Fig.4).

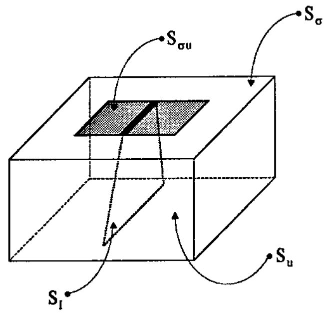

Fig. 4: Schematic representation of acousto-mechanical imaging setup.

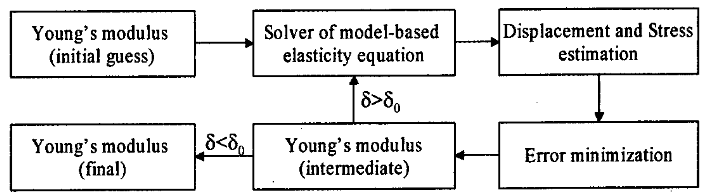

Fig. 5: Block-diagram of elasticity reconstruction procedure implemented in acousto-mechanical imaging. Both displacement and stress measurements are used simultaneously to estimate Young's modulus distribution within the imaging plane.

Determining the elastic modulus in inhomogeneous material from responses to a fixed mechanical action is possible by using a number of formulations [Skovoroda et al 1995 and 1999a]. For example, in ultrasound elasticity imaging, if all necessary components of the internal strain are measured, then reconstruction algorithms based on the mechanical equilibrium equations can be used to describe the unknown distribution of relative elasticity without additional assumptions. However, if any assumptions about the object can be made, then a more robust model-based reconstruction can be performed [Emelianov et al 1998]. Indeed, most of the breast lesions can be modeled as rounded inclusions. Therefore, the model of an elastic sphere in a heterogeneous background can be used. Since this elasticity imaging approach assumes a straightforward model such as this, reconstruction in the vicinity of the lesion is far less susceptible to noise. We have already developed [Skovoroda et al 1994; Sarvazyan and Skovoroda 1996; Skovoroda and Sarvazyan 1999] and successfully applied the model-based reconstruction approach to study elasticity imaging [Emelianov et al 1998]. This model is based on general theory of elasticity for incompressible medium. Indeed, most soft tissues are incompressible materials with Poisson's ratio approaches 0.5 [Sarvazyan et al 1995].

Comparing different approaches and techniques in elasticity reconstruction, we adopted the model-based quantitative elasticity reconstruction method (Fig. 5). Specifically, the unknown distribution of Young's modulus is reconstructed based on the simultaneous and synchronized measurement of normal stress at the surface $S_{\sigma u}$ and internal displacement within the ultrasound imaging plane S_I. As illustrated in Fig. 5, the iterative elasticity reconstruction starts with initial guess of Young's modulus distribution. The displacement, strain and stress fields are then computed using analytical solution of the model-based equilibrium equation. With every iteration, the elasticity distribution is adjusted to minimize the global error δ:

$$\delta = \int_{S_I} (u_l - u_l^*)^2 ds + \int_{S_u} \sum_{i=1}^{3} (u_i - u_i^*)^2 ds + \int_{S_{\sigma u}} \sum_{i=1}^{3} \left[(u_i - u_i^*)^2 + \Big(\sum_{j=1}^{3} (\sigma_{ij} - \sigma_{ij}^*) n_j\Big)^2 \right] ds + \int_{S_\sigma} \sum_{i=1}^{3} \Big(\sum_{j=1}^{3} (\sigma_{ij} - \sigma_{ij}^*) n_j\Big)^2 ds ,$$

where the measured or otherwise known parameters are denoted with asterisk, u_l and u_l^* are model-predicted and ultrasonically measured axial displacement in the imaging plane, and nj is the j[th] component of the unit normal vector at the surface $S_{\sigma u}$, S_σ and S_u are the surface of the tactile sensor, the remaining top surface, and the bottom surface of the breast, respectively (the geometry is schematically presented in Fig. 4). In most cases of

breast tactile imaging, the σ_{ij}^{*} at the S_{σ} surface will be set to zero. Similarly, the displacements u_i^{*} at the bottom surface S_u are also zero. By itself, the measured internal displacement provides additional stability of the error minimization procedure. Moreover, compared to mechanical imaging system, the ultrasound B-Scan can provide the overall geometry of the breast and possibly the geometry and location of the lesion – this information can be used both to refine initial Young's modulus guess and to enhance the elasticity minimization procedure. Once the minimization condition $\delta<\delta_0$ is reached, the resulting elasticity distribution is outputted to outline both absolute Young's modulus values and geometry of the identified lesion. Then, the elasticity image within ultrasound imaging plane can be further refined.

An example of elasticity reconstruction is presented in Fig. 6. The reconstruction approach was tested on the tissue mimicking phantoms. Originally, a homogeneous 100-mm by 70-mm by 140-mm (WxHxL) gel was made with mechanical characteristics simulating breast tissue. The phantom was constructed from 6% by weight gelatin. During the construction, a 30-mm diameter circular hole was left in the center of the phantom. This hole was then filled with 12% by weight gelatin while another 20-mm diameter hole was kept approximately in the middle. Finally, the remaining hole was filled with 8% by weight gelatin. This lesion was simulating a two-stage lesion where the core of the lesion is slightly softer than the coat around it. The phantom was deformed in vertical direction while data for acousto-mechanical imaging were captured. Prior to reconstruction, the region of interest containing a small portion of background material, and the entire lesion was selected as shown in Fig. 6a. The corresponding axial strain image is presented in Fig. 6b, and reconstructed elasticity image is displayed in Fig. 6c with the display dynamic range given in a colorbar. Clearly, reconstruction depicted correct elasticity values for background (the most outer layer) and composite lesion. In fact, the elasticity variations closely correspond to the differences in gelatin concentration used to construct different portions of the phantoms. This example (Fig. 6), therefore, demonstrates that details of the elasticity distribution can be examined using model-based reconstruction approach.

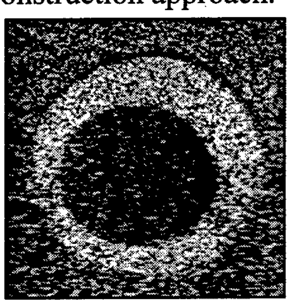

Fig. 6A: B-Scan image of the phantom with heterogeneous inclusion.

Fig. 6B: Image of axial strain within the phantom.

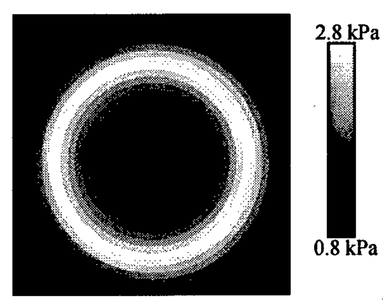

Fig. 6C: Reconstructed elasticity map depicting the variations of elasticity.

Viscosity Assessment using Stress Relaxation Imaging

During acousto-mechanical imaging, not only elasticity but also a viscosity can be potentially imaged. Indeed, the can be quickly compressed and then immobilized while ultrasound is used to carefully maintain and control the deformed state. However, once the compression is applied, the tissue reaches mechanical equilibrium not instantaneously – the rate depends on tissue viscosity. Therefore, if stress relaxation of the breast tissue can be captured, the maps of tissue viscosity could be obtained. We have initially studied

two tissue mimicking phantoms made out of gel and soft rubber to investigate whether sensitivity of pressure sensors is sufficient to measure stress relaxation and whether stress relaxation differ between the materials signaling of viscosity differences. The results of the study demonstrate that gel relaxes at a slower rate (Fig. 7a) compared to soft rubber (Fig. 7b) indicating elevated viscosity in gel. Finally, we have performed similar experiment of the forearm muscle (Fig. 7c)

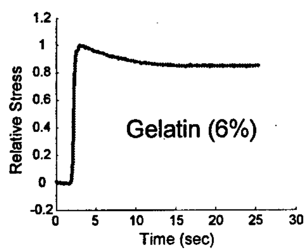

Fig. 7a: Stress relaxation of gelatin

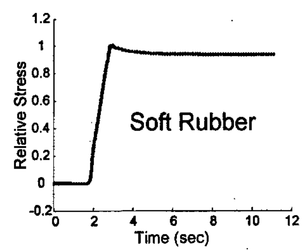

Fig. 7b: Stress relaxation of rubber

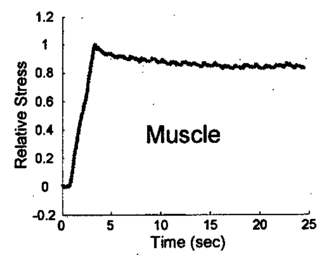

Fig. 7c: Stress relaxation of muscle tissue

Given the results of this experiment, it is possible to evaluate the viscosity of breast – the parameter that maybe highly sensitive to breast tissue pathology. Tissue viscosity is an independent tissue parameter [Duck 1991] that can be an image contrast mechanism. The viscosity of breast and other types of tissue is scarcely discussed in literature primarily due to inability of measuring viscosity without significant complications and more likely interference with clinical procedures – the stress relaxation is a natural fit to the ultrasound examination procedure. Note that stress relaxation and viscosity imaging was not originally proposed.

Prototype of the AMI imaging system:

The initial prototype of the acousto-mechanical imaging system was built within this project to demonstrate the feasibility of the technique. However, a custom designed and built stress imaging system was interfaced with available commercial ultrasound imaging system. Consequently, not every component of ultrasound imager was available for modification and tuning. However, in order for AMI to become a clinical tool, the stress imaging and ultrasound imaging systems must be fully integrated into one device. We are currently pursuing such development integrating all electronic components onto one printed circuit board. Once developed, the system will be able to perform both ultrasound speckle tracking based strain imaging and stress pattern mapping while displaying the intermediate and final results. Once the data is captured under interactive guidance, final elasticity reconstruction will be performed to complete the examination.

KEY RESEARCH ACCOMPLISHMENTS:

- Design, development and fabrication of pressure sensor array for acousto-mechanical imaging (in cooperation with Pressure Profile Systems, Inc. and Artann Laboratories, Inc.)
- Development of stress data acquisition circuitry including digital interface for PC-based data capture (in collaboration with Artann Laboratories, Inc.)
- Development of data acquisition software including user friendly graphical interface (in collaboration with Artann Laboratories, Inc.)
- Design and fabrication of breast mimicking tissue models (in collaboration with Artann Laboratories, Inc.)

- Development of model-based elasticity reconstruction algorithm
- Integration and synchronization of all components of the acousto-mechanical imaging system (in collaboration with Artann Laboratories, Inc.)
- Design and development of a prototype of the acousto-mechanical imaging system (in collaboration with Artann Laboratories, Inc.)

REPORTABLE OUTCOMES:

Skovoroda AR, Aglyamov SR, Sarvazyan AP, and Emelianov SY, "Acousto-mechanical imaging: assessment and validation using analytical and numerical modeling," IEEE Transactions on Medical Imaging, 2003 (submitted for publication).

Aglyamov SR, Skovoroda AR, Rubin JM, O'Donnell M, and Emelianov SY, "Model based reconstructive elasticity imaging of deep venous thrombosis," submitted for publication to the IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control (2003).

"Stress/Strain Elasticity Imaging" – SBIR phase I and II grant proposal, PI: Dr. J. Son (submitted to NIH, July 2003)

CONCLUSIONS:

Acousto-mechanical imaging digitally captures the human sense of touch to provide maps of the underlying tissue structure in terms of its mechanical properties. As described above, this modality may have far greater sensitivity than manual palpation over a representative range of lesion sizes and depths. Moreover, it can detect the impalpable lesions thus extending the limited range of manual breast examination. Therefore, the acousto-mechanical imaging holds great promise for improving early detection and diagnosis of breast cancers. This promise is greatly amplified by relatively simple and inexpensive implementation of the acousto-mechanical imaging – an adjunct to the existing imaging studies of the breast. In addition, 3-D visualization is possible in acousto-mechanical imaging – this can find a broad range of clinical applications ranging from improved breast biopsy procedures to quantitative evaluation of breast masses and composition. Finally, because of the correlation between the mechanical and histopathological properties of lesions, the acousto-mechanical imaging can provide a mean for non-invasive detection and differentiation of breast pathology.

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APPENDICES:

None